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(54) Title: PROCESS FOR THE PREPARATION OF VALSARTAN

(57) Abstract: Provided is a process for preparing valsartan substantially free of its isoleucine analogue and precursor thereof. The process for preparing valsartan comprising the step of: a) obtaining one or more samples of at least a single valine or valine derivative batch; b) measuring the level of isoleucine or corresponding isoleucine derivative in each of the samples of step (a); c) selecting the batch of valine or its derivative that comprises a level of isoleucine or isoleucine derivative of less than about 0.1% as area percentage GC based on the measurement or measurements conducted in step (b); and d) using the batch selected in step (c) to synthesize said valsartan.

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PROCESS FOR THE PREPARATION OF VALSARTAN

PRIORITY

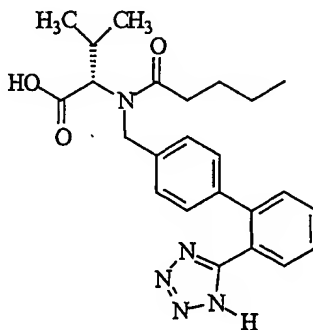
5 This application claims the benefit of U.S. provisional application Serial No. 60/537,994, filed January 21, 2004; U.S. provisional application Serial No. 60/_____, filed March 30, 2004; U.S. provisional application Serial No. 60/512,557, filed October 16, 2003; U.S. provisional application Serial No. 60/471,871, filed May 20, 2003; and
10 U.S. provisional application Serial No. 60/464,197, filed April 21, 2003, the contents of all of which are incorporated herein.

FIELD OF THE INVENTION

15 The present invention relates to a process for preparing valsartan and precursors thereof.

BACKGROUND

20 Valsartan, also known as (S)-N-(1-Carboxy-2-methyl-prop-1-yl)-N-pentanoyl-N-[2'-(1H-tetrazol-5-yl)bi phenyl-4-ylmethyl]-amine, has the following structure:



Formula	C ₂₄ H ₂₉ N ₅ O ₃
Molecular Mass	435.52
Exact Mass	435.227040
Composition	C 66.19% H 6.71% N 16.08% O 11.02
Melting Range	105 - 110°C

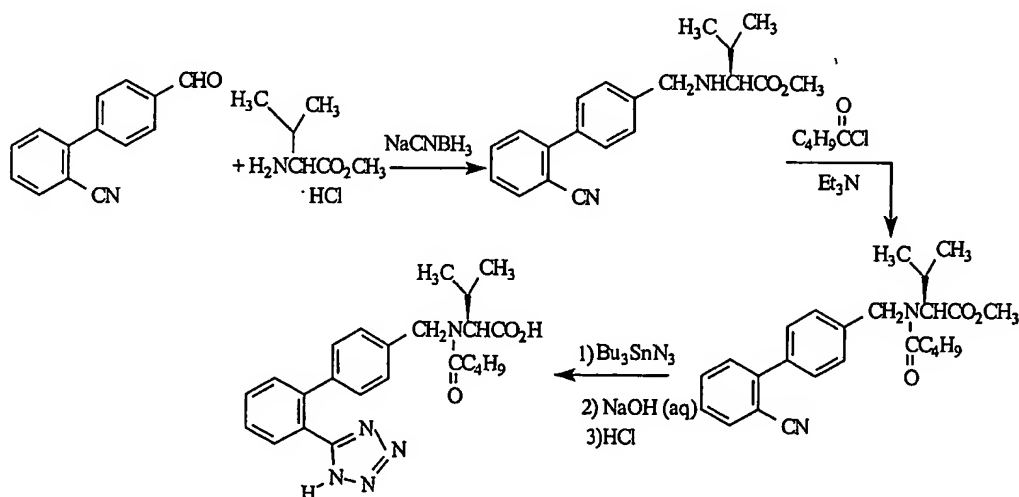
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and is marketed as the free acid under the name DIOVAN. DIOVAN is prescribed as oral tablets in dosages of 40 mg, 80 mg, 160 mg and 320 mg of valsartan.

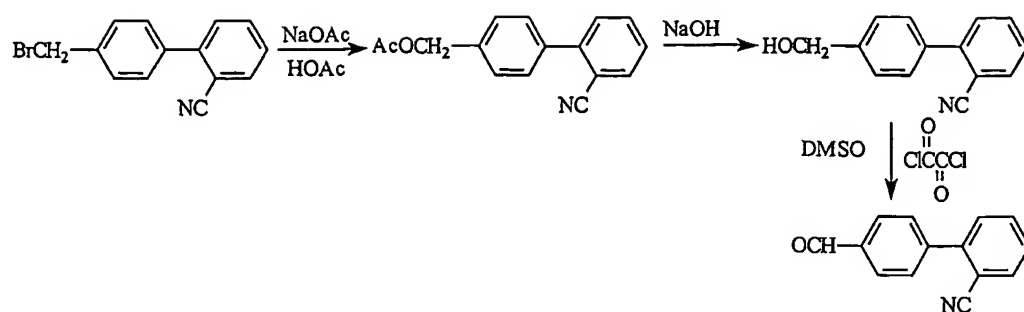
Valsartan and/or its intermediates are disclosed in various references, including:
 U.S. Pat. Nos. 5,399,578, 5,965,592, 5,260,325, 6,271,375, WO 02/006253, WO
 01/082858, WO 99/67231, WO 97/30036, Peter Bühlmayer, et. al., Bioorgan. & Med.
 Chem. Let., 4(1) 29-34 (1994), Th. Moenius, et. al., J. Labelled Cpd. Radiopharm., 43(13)
 1245 – 1252 (2000), and Qingzhong Jia, et. al., Zhongguo Yiyao Gongye Zazhi, 32(9)
 385-387 (2001).

Valsartan is an orally active specific angiotensin II antagonist acting on the AT1
 receptor subtype. Valsartan is prescribed for the treatment of hypertension. U.S. Pat. No.
 6,395,728 is directed to use of valsartan for treatment of diabetes related hypertension.
 U.S. Pat. Nos. 6,465,502 and 6,485,745 are directed to treatment of lung cancer with
 valsartan. U.S. Pat. No. 6,294,197 is directed to solid oral dosage forms of valsartan.
 These patents are incorporated herein by reference.

The synthesis of valsartan is discussed, inter alia, in United States Patent No.
 5,399,578, which is incorporated herein in its entirety by reference. In the synthesis
 disclosed therein, the final synthetic step (exclusive of work-up and purification) involves
 the reaction of a cyano group on the biphenyl ring with an azide, for example, tributyl tin
 azide. The reaction scheme of the '578 patent is as follows:

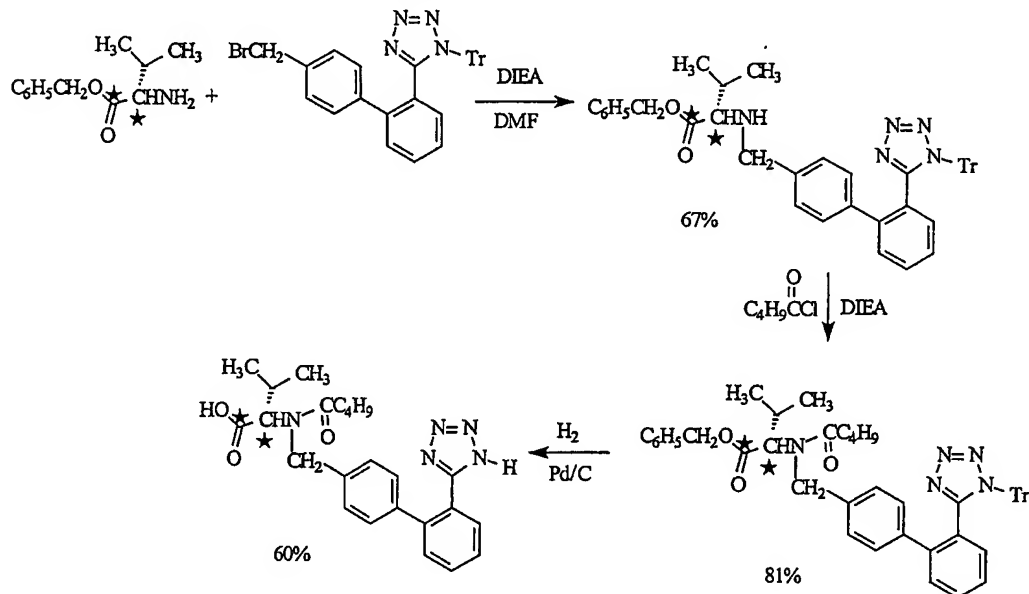


The starting compound in the '578 patent is made as follows:

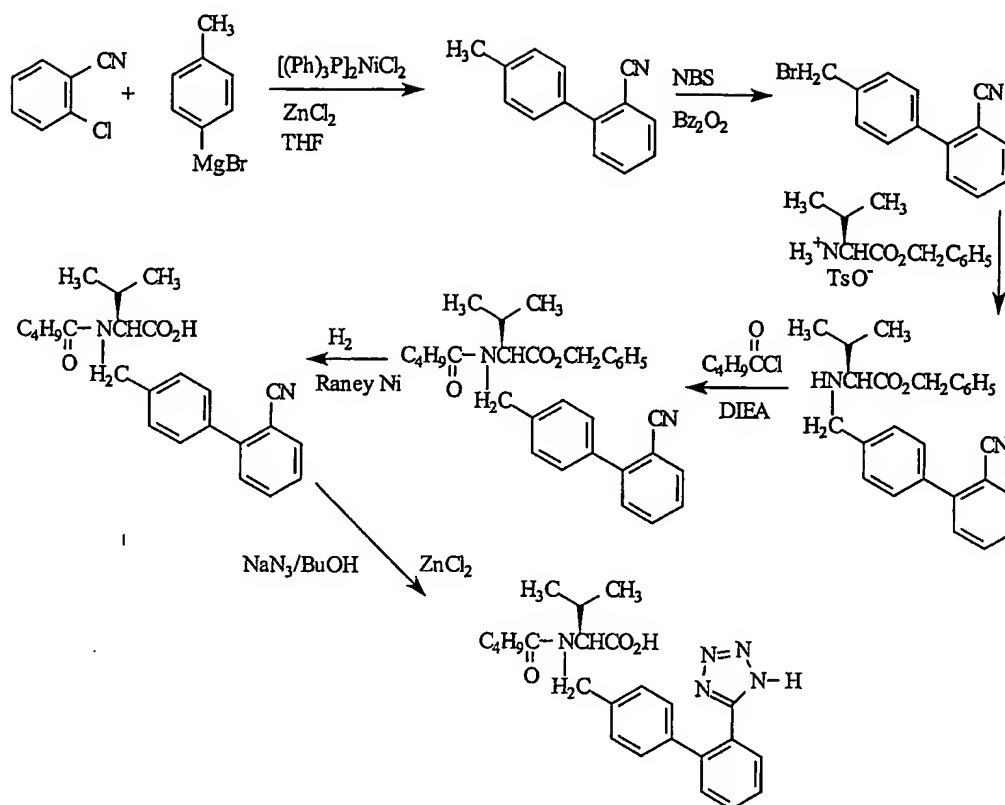


Peter Bühlmayer, et. al., *Bioorgan. & Med. Chem. Let.*, **4**(1) 29-34 (1994)

- 5 In Moenius, et. al., *J. Labelled Cpd. Radiopharm.*, **43**(13) 1245 – 1252 (2000), various schemes for synthesis of valsartan are provided, with one being:



- 10 Another paper, Qingzhong Jia, et. al., *Zhongguo Yiyao Gongye Zazhi*, **32**(9) 385-387 (2001), discloses a synthesis scheme for valsartan as follows:



There is a need in the art for an improved synthetic process for the preparation of valsartan and precursors of valsartan.

5

OBJECTS AND SUMMARY OF THE INVENTION

In one embodiment, the present invention provides valsartan substantially free of its isoleucine analogue.

10

In another embodiment, the present invention provides a method for preparing valsartan substantially free of its isoleucine analogue. This method includes starting with a sample of valine or valine derivative, preferably L-valine methyl ester, comprising a sufficiently low level of the isoleucine derivative, preferably L-isoleucine methyl ester.

15 Preferably, the amount of the isoleucine derivative in the valine or valine derivative sample is less than about 0.1% as rear percentage GC. This method comprises:

- a) obtaining one or more samples of one or more batches of valine or its derivative;

- b) measuring the level of isoleucine or corresponding isoleucine derivative in each of the samples of step (a);
- c) selecting the valine or valine derivative batch that comprises a level of isoleucine or isoleucine derivative of less than about 0.1% as area percentage GC based on the measurement or measurements conducted in step (b); and
- 5 d) using the batch selected in step (c) to synthesize said valsartan.

In a preferred embodiment, the valine or valine derivative sample has an amount of less than about 0.07% as area percentage GC of its isoleucine analogue.

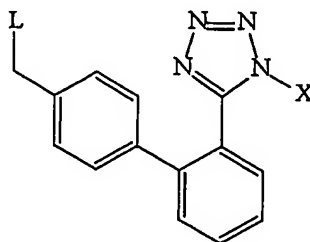
The level of the isoleucine derivative in the valine sample can be determined using standard analytical techniques known to those of ordinary skill in the art. For example, the level of the isoleucine derivative may be determined by GC.

Valsartan is synthesized by methods such as described in U.S. patent no. 5,399,578, hereby incorporated by reference.

In another aspect, the present invention provides a process for preparing valsartan comprising synthesizing valsartan from a sample of valine or a valine derivative, wherein the process analyzes the level of isoleucine or its derivative present in an initial sample of valine or its derivative at least at a single stage during the synthetic process to control amount of the corresponding isoleucine impurity present in valsartan.

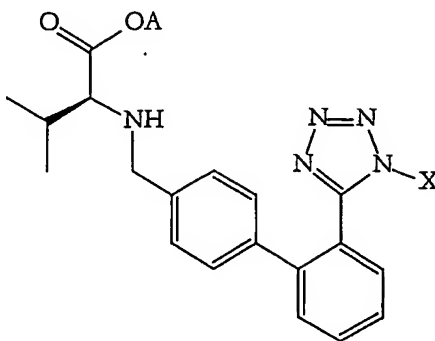
In another aspect, the present invention provides a process for preparing valsartan comprising the steps of:

- a) analyzing a C₁ to C₄ alkyl ester of L-valine for presence of its isoleucine analogue as an impurity;
- b) selecting a sample that has NMT about 0.1% as area percentage GC of the isoleucine analogue of L-valine as determined by HPLC;



c) reacting compound G2:

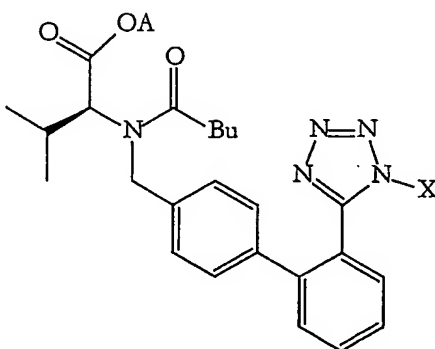
with the L-valine ester in a first organic solvent to obtain a compound G3:



G3

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d) reacting compound G3 with an acylating agent in a second organic solvent to obtain a compound G4;



G4

and

10

e) hydrolyzing compound G4 to obtain valsartan.

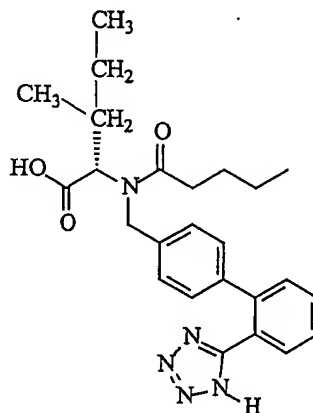
wherein A is a C₁ to C₄ alkyl ester, X is a trityl group and L is a leaving group.

DETAILED DESCRIPTION OF THE INVENTION

15

The levels of isoleucine analogue of valine were analyzed by GC. The levels of isoleucine analogue in valsartan were analyzed by HPLC.

The presence of impurities in valsartan may pose a problem for formulation in that impurities often affect the safety and shelf life of a formulation. The present invention provides a method for ameliorating the effect of a single impurity present in formulations of valsartan by reducing the amount of the impurity during synthesis. The impurity, the
5 isoleucine analogue of L-valine, has not been disclosed in the literature and has the following structure:



Two samples of Valsartan were prepared by the described procedure (examples 1-3) of the present invention from Valine Methyl ester of different suppliers. The sample
10 from supplier A contained 0.131% as area percentage GC of isoleucine methyl ester and the sample from supplier B (Kony Pharma China) contained 0.07% as area percentage GC of the ester by GC as area percentage (for method see analytical part). The Valsartan prepared from valine methyl ester of supplier A contained 0.13% as area percentage HPLC of isoleucine analogue and valsartan prepared from supplier B contained 0.07 % as
15 area percentage HPLC of the isoleucine analogue (for HPLC method see analytical part). These results are in good correlation with GC data of the starting Valine Methyl Esters, suggesting that the isoleucine impurity present in the starting material would also be present in the final product in the same ratio.

20 Accordingly, the present invention provides a process for preparing valsartan having a low level of the isoleucine analogue as an impurity by checking for the impurity in the starting material and choosing starting material which has a low level of the impurity. See e.g. WO/03070246, incorporated herein by reference. In one embodiment, a sample of VLS-07 having a level of the impurity of NMT about 0.1% as area

percentage GC, more preferably NMT about 0.07% is chosen. The relative retention time (RRT) of the isoleucine analogue of VLS-07 compared to VLS-02 is 1.2. Instead of choosing VLS-07, other batches of intermediates such as VLS-04 and VLS-05 may be tested for the amount of the impurity, and the batches discarded if the requisite amount of
5 impurity is not met.

If the requisite amount of impurity is not met, it may be possible to purify the starting material or intermediates by techniques such as crystallization. *See e.g.* WO/03070246.

10

The method of the present invention may be applied to any synthesis method known in the art, such as that disclosed in U.S. Pat. No. 5,399,578. In a preferred embodiment illustrated in the present invention, the synthesis of valsartan is carried out by reacting a 5-(4'-bromomethylbiphenyl-2-yl)-1H-tetrazole with an L-valine derivative
15 substantially free of its isoleucine analogue. The L-valine derivative may be any suitable derivative, including but not limited to addition salts, ethers and esters of L-valine. Preferred esters include methyl, ethyl, propyl, butyl (including t-butyl), benzyl and aryl esters. A most preferred ester is a C₁ to C₄ alkyl ester, particularly methyl or t-butyl ester.

20 The reaction is preferably carried out in an organic solvent. Examples of preferred organic solvents include, but are not limited to, N,N dimethyl formamide (DMF), dimethyl acetamide (DMA), toluene, hexane, 1,2-dimethoxyethane (DME), diethoxymethane, tetrahydrofuran (THF), benzene, m-xylene, ethyl acetate, o-xylene, tetralins, formals, glymes and mixtures thereof. Other hydrocarbons useful in the practice
25 of the present invention will be apparent to the skilled artisan.

The synthesis of valsartan of the present invention may include the step of reacting a 5-(4'-bromomethylbiphenyl-2-yl)-1H-tetrazole with an L-valine derivative. A preferred 5-(4'-bromomethylbiphenyl-2-yl)-1H-tetrazole is 5-(4'-bromomethylbiphenyl-2-yl)-1-trityl-1H-tetrazole (VLS-02). A preferred L-valine derivative is L-valine methyl
30 ester (VLS-07). The step is carried out in an organic solvent reaction system. To the organic solvent is added an amount of a basic material. The basic material may be a carbonate salt of an alkali metal or an organic base. Preferred salts of alkali metals include

sodium carbonate and potassium carbonate. Preferred organic bases include triethanolamine, diethanolamine, triethylamine and diethylamine. As described above the organic solvent is preferably selected from DMF, DMA, toluene, hexane, DME, diethoxymethane, THF, benzene, m-xylene, o-xylene, ethyl acetate, tetralins, formals, glymes and mixtures thereof. A most preferred organic solvent is acetonitrile. The reaction may optionally be carried out in the presence of a catalyst. Preferred solvents for use with a phase transfer catalyst are toluene and ethyl acetate. VLS-07 is added to the solvent/base mixture. VLS-02 is added, preferentially in three separate portions, to the reaction mixture, and the resulting reaction mixture is heated with agitation for a reaction time of between 1 to 6 hours.

After the reaction time, the reaction system is cooled, and the solvent is removed to yield the crude residue of N-valine methyl ester 5-(4'-methylbiphenyl-2-yl)-1-trityl-1H-tetrazole reaction product (VLS-04). Typically the solvent is removed by evaporation under reduced pressure.

In addition to bromine in VLS-02, other leaving groups may be utilized, including other halogens such as chlorine, or sulfonates. The acylating agent used may also include other leaving groups.

In a second step of the synthetic method of the present invention, the N-valine methyl ester 5-(4'-methylbiphenyl-2-yl)-1-trityl-1H-tetrazole reaction product (VLS-04) is reacted with an acylating agent to form a valsartan precursor such as (S)-N-(1-carboxymethoxy-2-methyl-prop-1-yl)-N-pentanoyl-N-[2'-(1-trityl-1H-tetrazol-5-yl)biphenyl-4-yl methyl]-amine (VLS-05). Crude residue produced in the synthetic step described above is dissolved in a suitable organic solvent. The organic solvent preferably contains an amount of an organic basic material. Preferred organic basic materials include triethylamine and tributylamine. Preferred organic solvents include toluene, DMA, DMF, hexane and acetonitrile. A most preferred organic solvent is dry toluene. To the resulting solution is added an acylating agent. Preferably the acylating agent is valeroyl chloride. The resulting mixture is agitated at room temperature for a period of from about 12 to about 24 hours. Preferably the reaction mixture is agitated for a period of about 20 hours. The time of the acylation reaction can be conveniently monitored using thin layer

chromatography. Following completion of the reaction, the reaction mixture is neutralized with a molar excess of base, preferably aqueous NaHCO₃, and the resulting two-phase reaction system is separated. The organic phase is washed and dried, and the reaction product, (S)-N-(1-carboxymethoxy-2-methyl-prop-1-yl)-N-pentanoyl-N-[2'-(1-trityl-1H-tetrazol-5-yl)biphenyl-4-yl methyl]-amine, (VLS-05), separated out. The separation may be carried out by any known method, but is typically carried out by evaporation under reduced pressure. The reaction product may be purified by, for example, chromatographic means, prior to further use in the synthesis.

10 In a third step of the synthetic method of the present invention the protecting groups, e.g., the trityl group attached to the tetrazole ring and the L-valine substituent (such as the methyl ester group of L-valine methyl ester (VLS-07)), can be cleaved to produce valsartan (VLS-00), or an analogue thereof. Crude residue produced in the synthetic step described above is dissolved in a suitable water-miscible solvent. A solvent
15 is water miscible if it is miscible with water at least in any proportion from 80:20 to 20:80 (weight basis). Preferred water-miscible solvents include acetone, methyl ethyl ketone (MEK), acetonitrile, tetrahydrofuran (THF), dioxane and C₁ to C₄ alcohols. Acetone is a most preferred water-miscible solvent. The resulting solution is acidified and agitated at a temperature of from about 0°C to about 40°C. Most preferably the temperature is about
20 room temperature. The time of the cleavage reaction can be conveniently monitored using thin layer chromatography. An aqueous solution of a basic material is added and the water-miscible solvent is evaporated, preferably at reduced pressure. Suitable basic materials include potassium hydroxide, potassium carbonate and sodium hydroxide. The trityl alcohol formed is separated and the liquid phase is acidified by addition of a suitable
25 acid to a pH of about 3. Preferred acids include mineral acids, hydrogen sulfate, trifluoroacetic acid, formic acid, hydrobromic acid and acetic acid. A most preferred acid is hydrochloric acid. The resulting suspension is extracted with ethyl acetate and the crude product, for example, (S)-N-(1-carboxymethoxy-2-methyl-prop-1-yl)-N-pentanoyl-N-[2'-(1H-tetrazol-5-yl) biphenyl-4-yl methyl]-amine, (VLS-06), recovered by, for example,
30 evaporation under reduced pressure. The resulting product is dissolved in an organic solvent. Preferred organic solvents include organic alcohols, acetone and acetonitrile. A most preferred solvent is acetone. The resulting solution is cooled to a temperature of between about -10°C and about 45°C. Preferably the resulting solution is cooled to a

temperature of between about 0°C and about 4°C. The acid is neutralized with a molar excess of base, preferably aqueous KOH, and the water-miscible solvent is evaporated, preferably at reduced pressure. The time of the cleavage reaction can be conveniently monitored using thin layer chromatography or HPLC monitoring. The solution is
5 extracted with ethyl acetate and acidified by addition of a suitable acid to a pH of about 3. Preferred acids include mineral acids, hydrogen sulfate, trifluoroacetic acid, formic acid, hydrobromic acid and acetic acid. A most preferred acid is hydrochloric acid. The resulting suspension is cooled and the product recovered by, for example, filtration. If desired, the isolated product can be washed with water, and dried, preferably at reduced
10 pressure.

Some of the steps of the present invention may be carried out in one pot, as illustrated in the examples.

15 The valsartan synthesized may be obtained as various polymorphic forms in the solid state. Such forms are disclosed in U.S. Appl. No. 60/455,286, Filed on March 17, 2003, entitled "Polymorphs of Valsartan and Processes for their Preparation", which is incorporated herein by reference.

20 Crude valsartan may be crystallized from organic solvents such as dichloromethane, diethyl ether or ethyl acetate. In a preferred embodiment, valsartan is crystallized from ethyl acetate. When crude material is crystallized out of ethyl acetate, the dry material may contain about 2.7% ethyl acetate by weight after conventional drying. The present invention provides for removing residual organic solvent such as ethyl acetate
25 from the crude material. The crude valsartan, either wet or dry, preferably wet, containing residual solvent is triturated in water, in order to remove the residual solvent to acceptable levels (according to the ICH guidelines the level is limited to less than about 5000 ppm). In one embodiment, after trituration in water, the level of the residual solvent is 3600 ppm. Preferably the trituration is performed from about 4 to about 50°C, more preferably from
30 about 25 to about 40°C. Preferably, the trituration is carried out for about 30 minutes to about 60 hours, more preferably from about 3 to about 20 hours.

Another manner to remove residual solvent, particularly ethyl acetate, is by performing a solvent exchange by contacting the solvate with humid gas in a fluidized bed apparatus. As used herein, the term "humid" refers to a relative humidity of at least 30%, more preferably at least about 50% and most preferably at least about 80%. A suitable
5 fluidized bed apparatus is Retsch TG-100.

Pharmaceutical formulations/compositions of the present invention contain crystalline valsartan, such as one of those disclosed in U.S. Appl. No. 60/455,286, Filed on March 17, 2003, entitled "Polymorphs of Valsartan and Processes for their Preparation",
10 or valsartan purely amorphous, optionally in mixture with other form(s) of valsartan. The valsartan prepared by the processes of the present invention are ideal for pharmaceutical formulation since they are substantially free of the isoleucine analogue as an impurity. In addition to the active ingredient(s), the pharmaceutical compositions of the present invention may contain one or more excipients. Excipients are added to the composition
15 for a variety of purposes.

Diluents increase the bulk of a solid pharmaceutical composition, and may make a pharmaceutical dosage form containing the composition easier for the patient and care giver to handle. Diluents for solid compositions include, for example, microcrystalline
20 cellulose (e.g. Avicel[®]), microfine cellulose, lactose, starch, pregelatinized starch, calcium carbonate, calcium sulfate, sugar, dextrates, dextrin, dextrose, dibasic calcium phosphate dihydrate, tribasic calcium phosphate, kaolin, magnesium carbonate, magnesium oxide, maltodextrin, mannitol, polymethacrylates (e.g. Eudragit[®]), potassium chloride, powdered cellulose, sodium chloride, sorbitol and talc.

25

Solid pharmaceutical compositions that are compacted into a dosage form, such as a tablet, may include excipients whose functions include helping to bind the active ingredient and other excipients together after compression. Binders for solid
pharmaceutical compositions include acacia, alginic acid, carbomer (e.g. carbopol),
30 carboxymethylcellulose sodium, dextrin, ethyl cellulose, gelatin, guar gum, hydrogenated vegetable oil, hydroxyethyl cellulose, hydroxypropyl cellulose (e.g. Klucel[®]), hydroxypropyl methyl cellulose (e.g. Methocel[®]), liquid glucose, magnesium aluminum

silicate, maltodextrin, methylcellulose, polymethacrylates, povidone (e.g. Kollidon[®], Plasdone[®]), pregelatinized starch, sodium alginate and starch.

The dissolution rate of a compacted solid pharmaceutical composition in the patient's stomach may be increased by the addition of a disintegrant to the composition. Disintegrants include alginic acid, carboxymethylcellulose calcium, carboxymethylcellulose sodium (e.g. Ac-Di-Sol[®], Primellose[®]), colloidal silicon dioxide, croscarmellose sodium, crospovidone (e.g. Kollidon[®], Polyplasdone[®]), guar gum, magnesium aluminum silicate, methyl cellulose, microcrystalline cellulose, polacrillin potassium, powdered cellulose, pregelatinized starch, sodium alginate, sodium starch glycolate (e.g. Explotab[®]) and starch.

Glidants can be added to improve the flowability of a non-compacted solid composition and to improve the accuracy of dosing. Excipients that may function as glidants include colloidal silicon dioxide, magnesium trisilicate, powdered cellulose, starch, talc and tribasic calcium phosphate.

When a dosage form such as a tablet is made by the compaction of a powdered composition, the composition is subjected to pressure from a punch and dye. Some excipients and active ingredients have a tendency to adhere to the surfaces of the punch and dye, which can cause the product to have pitting and other surface irregularities. A lubricant can be added to the composition to reduce adhesion and ease the release of the product from the dye. Lubricants include magnesium stearate, calcium stearate, glyceryl monostearate, glyceryl palmitostearate, hydrogenated castor oil, hydrogenated vegetable oil, mineral oil, polyethylene glycol, sodium benzoate, sodium lauryl sulfate, sodium stearyl fumarate, stearic acid, talc and zinc stearate.

Flavoring agents and flavor enhancers make the dosage form more palatable to the patient. Common flavoring agents and flavor enhancers for pharmaceutical products that may be included in the composition of the present invention include maltol, vanillin, ethyl vanillin, menthol, citric acid, fumaric acid, ethyl maltol and tartaric acid.

Solid and liquid compositions may also be dyed using any pharmaceutically acceptable colorant to improve their appearance and/or facilitate patient identification of the product and unit dosage level.

5 In liquid pharmaceutical compositions of the present invention, valsartan and any other solid excipients are dissolved or suspended in a liquid carrier such as water, vegetable oil, alcohol, polyethylene glycol, propylene glycol or glycerin.

10 Liquid pharmaceutical compositions may contain emulsifying agents to disperse uniformly throughout the composition an active ingredient or other excipient that is not soluble in the liquid carrier. Emulsifying agents that may be useful in liquid compositions of the present invention include, for example, gelatin, egg yolk, casein, cholesterol, acacia, tragacanth, chondrus, pectin, methyl cellulose, carbomer, cetostearyl alcohol and cetyl alcohol.

15 Liquid pharmaceutical compositions of the present invention may also contain a viscosity enhancing agent to improve the mouth-feel of the product and/or coat the lining of the gastrointestinal tract. Such agents include acacia, alginic acid bentonite, carbomer, carboxymethylcellulose calcium or sodium, cetostearyl alcohol, methyl cellulose, 20 ethylcellulose, gelatin guar gum, hydroxyethyl cellulose, hydroxypropyl cellulose, hydroxypropyl methyl cellulose, maltodextrin, polyvinyl alcohol, povidone, propylene carbonate, propylene glycol alginate, sodium alginate, sodium starch glycolate, starch tragacanth and xanthan gum.

25 Sweetening agents such as sorbitol, saccharin, sodium saccharin, sucrose, aspartame, fructose, mannitol and invert sugar may be added to improve the taste.

 Preservatives and chelating agents such as alcohol, sodium benzoate, butylated hydroxy toluene, butylated hydroxyanisole and ethylenediamine tetraacetic acid may be 30 added at levels safe for ingestion to improve storage stability.

 According to the present invention, a liquid composition may also contain a buffer such as guconic acid, lactic acid, citric acid or acetic acid, sodium guconate, sodium

lactate, sodium citrate or sodium acetate. Selection of excipients and the amounts used may be readily determined by the formulation scientist based upon experience and consideration of standard procedures and reference works in the field.

5 The solid compositions of the present invention include powders, granulates, aggregates and compacted compositions. The dosages include dosages suitable for oral, buccal, rectal, parenteral (including subcutaneous, intramuscular, and intravenous), inhalant and ophthalmic administration. Although the most suitable administration in any given case will depend on the nature and severity of the condition being treated, the most
10 preferred route of the present invention is oral. The dosages may be conveniently presented in unit dosage form and prepared by any of the methods well-known in the pharmaceutical arts.

 Dosage forms include solid dosage forms like tablets, powders, capsules,
15 suppositories, sachets, troches and lozenges, as well as liquid syrups, suspensions and elixirs.

 The dosage form of the present invention may be a capsule containing the composition, preferably a powdered or granulated solid composition of the invention, within either a hard or soft shell. The shell may be made from gelatin and optionally
20 contain a plasticizer such as glycerin and sorbitol, and an opacifying agent or colorant.

 The active ingredient and excipients may be formulated into compositions and dosage forms according to methods known in the art.

25 A composition for tableting or capsule filling may be prepared by wet granulation. In wet granulation, some or all of the active ingredients and excipients in powder form are blended and then further mixed in the presence of a liquid, typically water, that causes the powders to clump into granules. The granulate is screened and/or milled, dried and then screened and/or milled to the desired particle size. The granulate may then be tableted, or
30 other excipients may be added prior to tableting, such as a glidant and/or a lubricant.

 A tableting composition may be prepared conventionally by dry blending. For example, the blended composition of the actives and excipients may be compacted into a

slug or a sheet and then comminuted into compacted granules. The compacted granules may subsequently be compressed into a tablet.

As an alternative to dry granulation, a blended composition may be compressed
5 directly into a compacted dosage form using direct compression techniques. Direct
compression produces a more uniform tablet without granules. Excipients that are
particularly well suited for direct compression tableting include microcrystalline cellulose,
spray dried lactose, dicalcium phosphate dihydrate and colloidal silica. The proper use of
these and other excipients in direct compression tableting is known to those in the art with
10 experience and skill in particular formulation challenges of direct compression tableting.

A capsule filling of the present invention may comprise any of the aforementioned
blends and granulates that were described with reference to tableting, however, they are
not subjected to a final tableting step.

15

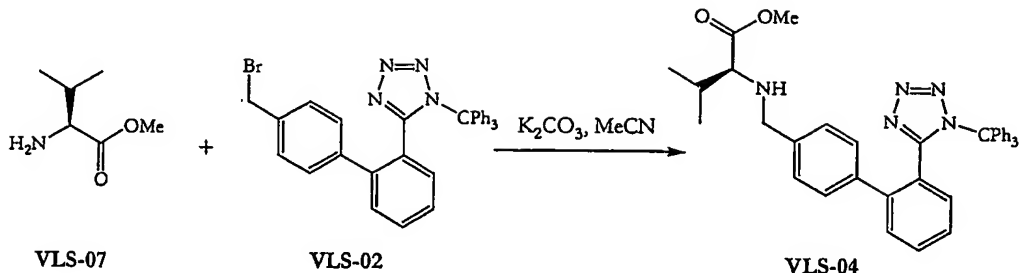
The solid compositions of the present invention include powders, granulates,
aggregates and compacted compositions. The dosages include dosages suitable for oral,
buccal, rectal, parenteral (including subcutaneous, intramuscular, and intravenous),
inhalant and ophthalmic administration. Although the most suitable route in any given
20 case will depend on the nature and severity of the condition being treated, the most
preferred route of the present invention is oral. The dosages can be conveniently
presented in unit dosage form and prepared by any of the methods well-known in the
pharmaceutical arts.

25 The active ingredient and excipients may be formulated into compositions and
dosage forms according to methods known in the art. The solid oral dosage forms
disclosed in U.S. Pat. Nos. 6,485,745 and 6,395,728 may be used as a guidance. The
dosages and formulation of DIOVAN may also be used for guidance. The dosage is
preferably from about 10mg to about 1280mg, more preferably from about 20mg to about
30 640mg, and most preferably from about 40mg to about 320mg.

The present invention can be illustrated in one of its embodiments by the
following non-limiting examples.

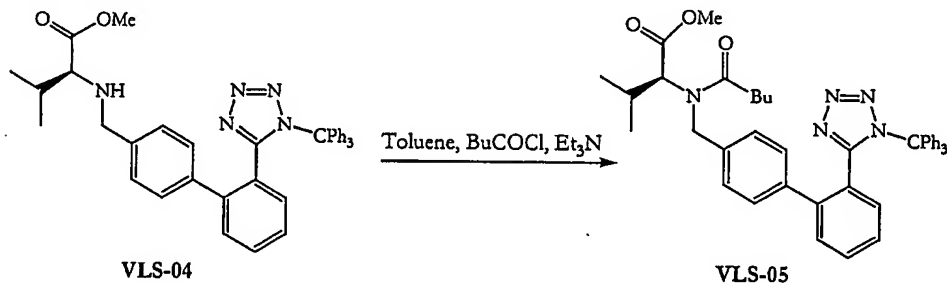
Preparation of Valsartan

Example 1

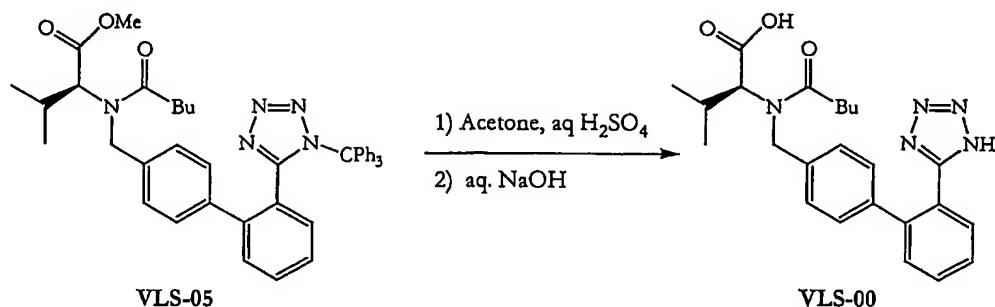


VLS-02 (30.0 g, 54.0 mmol) was added in one portion to the suspension of L-Valine methyl ester (free base, VLS-07, 10.6 g, 81.0 mmol, 1.5 eq) and K_2CO_3 (59.5g, 4.3 mol, 8 eq) in dry Acetonitrile (200 mL) preheated to 50-60 °C. The reaction was stirred for 2-3 h at 70 °C under Argon, cooled to 0 °C and filtered. The filtrate was evaporated under
 10 reduced pressure to give 36.0 g of crude VLS-04 as sticky yellow oil that was used in the next step without any purification.

Example 2



To solution of VLS-04 (36.0 g, 54 mmol) and Triethylamine (16.4 g, 22.5 mL, 162 mmol, 3.0 eq) in dry Toluene (200 mL) Valeroyl chloride (16.3 g, 16.0mL, 0.135 mmol, 2.5 eq) was slowly added under Argon keeping the reaction temperature below 35°C. The resulted mixture was stirred for 10 h at room temperature and quenched with 10 %
 20 aqueous solution of $NaHCO_3$ (100 mL). After stirring of 1 h at room temperature, the two-phase mixture was separated, the organic phase washed with 10 % aqueous solution of $NaHCO_3$ (50 mL) and brine, dried over Na_2SO_4 , filtered and evaporated under reduced pressure to give 44.0 g (near quant) of crude VLS-05 as yellow semisolid.

Example 3

VLS-05 (15.0 g, 21.7 mmol) was dissolved in Acetone (90 mL), H₂SO₄ (98%, 3.5 mL, ~3
5 eq) in Water (20 mL) was slowly added and the resulted cloud solution was stirred for 5 h
at room temperature (TLC or HPLC monitoring). A solution of NaOH (5.2 g, 130.2
mmol, 6 eq) in Water (10 mL) was slowly added, the resulted suspension was stirred for
12 h at room temperature and Acetone was evaporated under reduced pressure. The
precipitate (TPM) was filtered and washed with Water (20 mL); the combined aqueous
10 filtrate washed twice with total 50 mL of EtOAc and slowly acidified to pH 2.5 with 3N
aqueous H₂SO₄. The resulted suspension was extracted twice with EtOAc (total 120 mL),
the combined organics were washed with brine and concentrated to 50 mL volume under
reduced pressure. This solution was cooled down to 0-4 °C, stirred for 2 h and filtered to
give 7.2 g of crude VLS-00 as a white solid. The crude was recrystallized from EtOAc
15 afforded about 6.5 g of Valsartan as white powder.

Example 4

Two samples of VLS-07 were tested for the level of isoleucine impurity by gas
chromatography. One sample showed an impurity of 0.07%, another sample 0.30%. The
20 sample with 0.07% was selected for preparation of valsartan according to examples 1-3.

Example 5

Two samples of L-valine are tested for the level of isoleucine impurity by gas
chromatography. One sample shows an impurity of 0.07%, another sample 0.30%. The
25 sample with 0.07% is selected for preparation of valsartan according process of U.S. Pat.
No. 5,399,578.

Example 6

Two samples of VLS-07 are tested for the level of isoleucine impurity by gas chromatography. One sample shows an impurity of 0.07%, another sample 0.09%. Both samples are selected for preparation of valsartan according to examples 1-3.

5

**Analytical method for Valsartan:
Chromatography (HPLC)**

Column: Luna 5 μ m C18(2) 250 mm x 4.6 mm
10 (Phenomenex) Cat No. OOG-4252-EQ is suitable

Eluent: A: 0.1 % Trifluoroacetic Acid in Acetonitrile
B: 0.1 % Trifluoroacetic Acid in Water

15 **Gradient:** 0 min – 35 % A/65 % B, 15 min – 35 % A/65 % B
40 min – 80 % A/20 % B, 45 min – 80 % A/20 % B
Flow rate: 1.0 mL/min

Detector: UV at 215 nm

20

Column Temp.: 25 °C

Injection Vol.: 20 μ L

25 **Diluent:** Eluent Component A/Component B 50/50 (v/v)

Note: All solvents and reagents should be HPLC or analytical grade.

30

**Analytical method for L-Valine methyl ester
3.0 GC Parameters**

Column: DB-17 Capillary Column
35 Length - 30 m, ID – 0.53 mm

Stationary Phase - (50 %Phenyl)Methylpolysiloxane Film – 1 μ m

Temperature program:

40 Hold at 45 °C for 5 min, increase to 220 °C
at 10 °C per minute and hold at 220 °C for
4.5 min

Injector : 200 °C

45 **Detector:** FID

**Detector
temperature:** 250 °C

5 **Flow rate:** Carrier gas - Helium, about 1.9 mL/min

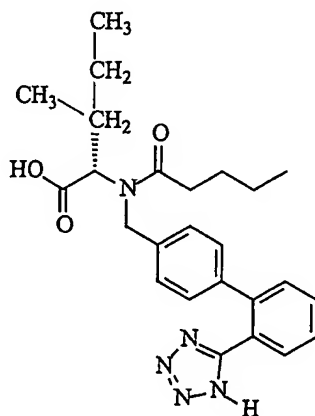
**Injection
volume:** 2.0 µL (split ratio 5:1)

10

Having thus described the invention with reference to particular preferred embodiments and illustrative examples, those in the art can appreciate modifications to the invention as described and illustrated that do not depart from the spirit and scope of the invention as disclosed in the specification. The Examples are set forth to aid in
15 understanding the invention but are not intended to, and should not be construed to, limit its scope in any way. The examples do not include detailed descriptions of conventional methods. Such methods are well known to those of ordinary skill in the art and are described in numerous publications. All references mentioned herein are incorporated in their entirety.

What is claimed is:

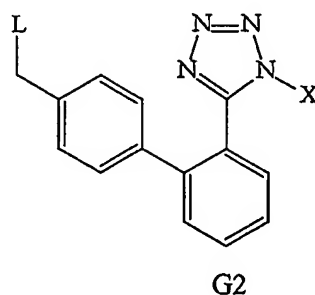
1. A process for synthesizing valsartan substantially free of its isoleucine analogue comprising the steps of:
 - a) obtaining one or more samples of at least a single valine or valine derivative batch;
 - b) measuring the level of isoleucine or corresponding isoleucine derivative in each of the samples of step (a);
 - c) selecting the batch of valine or its derivative that comprises a level of isoleucine or isoleucine derivative of less than about 0.1% as area percentage GC based on the measurement or measurements conducted in step (b); and
 - d) using the batch selected in step (c) to synthesize said valsartan.
2. The process of claim 1, wherein the valsartan contains less than about 0.1% as area percentage HPLC its corresponding isoleucine derivative.
3. The process of claim 2, wherein the level is 0.07%.
4. The process of claim 1, wherein the level of the isoleucine or the corresponding isoleucine derivative in the batch of valine or its derivative of step (c) is less than about 0.07% as area percentage GC.
5. A process for preparing valsartan comprising synthesizing valsartan from an initial sample of valine or a valine derivative, wherein the process analyzes the level of isoleucine or corresponding isoleucine derivative present in the initial sample at least at a single stage during the synthetic process to control amount of an impurity having the following structure:



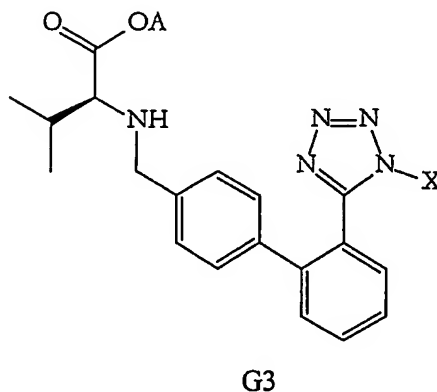
being present in valsartan.

6. The process of claim 5 wherein the desirable level of the isoleucine analogue is NMT 0.1% as area percentage HPLC.
7. The process of claim 1, 2, 3, 4, 5 or 6, wherein the analysis is carried out of the valine derivative in regard to its corresponding isoleucine derivative.
- 5 8. The process of claim 7, wherein the derivative that is analyzed is a methyl ester.
9. A process for preparing valsartan comprising the steps of:
- a) analyzing a C₁ to C₄ alkyl ester of L-valine for presence of its isoleucine analogue as an impurity;
- b) selecting a sample that has NMT about 0.1% as area percentage GC of the
10 isoleucine analogue of L-valine as determined by HPLC;
- c) reacting compound G2:

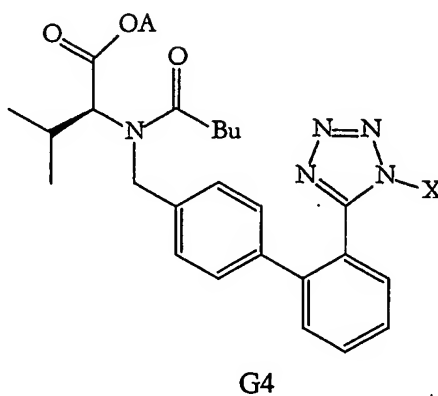
15



with the L-valine ester in a first organic solvent to obtain a compound G3:



reacting compound G3 with an acylating agent in a second organic solvent to obtain a compound G4;



5 and

e) hydrolyzing compound G4 to obtain valsartan.

wherein A is a C₁ to C₄ alkyl ester, X is a trityl group and L is a leaving group.

10. The process of claim 9, wherein the first and second organic solvents are independently selected from the group consisting of acetonitrile, toluene, acetone, ethyl acetate, dimethyl acetamide, DMF, hexane and mixtures thereof.
11. The process of claim 10, wherein step (c) is carried out in acetonitrile.
12. The process of claim 9, wherein the valsartan contains less than 0.1% of its corresponding isoleucine derivative as area percentage HPLC.
- 15 13. The valsartan prepared by the process of any of claims 1, 2, 3, 4, 5, 6, 9, 10, 11, or 12.
14. A pharmaceutical composition of valsartan comprising valsartan substantially free of its isoleucine analogue and a pharmaceutically acceptable excipient.
15. A method of lowering systematic blood pressure in a human in need thereof comprising the step of administering the pharmaceutical composition of claim 14 to the human.

INTERNATIONAL SEARCH REPORT

International Application No.
PCT/US2004/012780

A. CLASSIFICATION OF SUBJECT MATTER
IPC 7 C07D257/04

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 7 C07D

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

EPO-Internal, WPI Data

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	US 5 399 578 A (SCHMIDLIN TIBUR ET AL) 21 March 1995 (1995-03-21) cited in the application the whole document	1-15
X	MOENIUS T ET AL: "Carbon-14 Labelling of DIOVAN in its Valine-Moiety" JOURNAL OF LABELLED COMPOUNDS AND RADIOPHARMACEUTICALS, SUSSEX, GB, vol. 43, 2000, pages 1245-1252, XP002292105 ISSN: 0362-4803 cited in the application Page 1247, Scheme 2.	1-15
P, A	WO 03/070246 A (PFIZER PROD INC) 28 August 2003 (2003-08-28) cited in the application page 6, lines 9-12	1-15

☐ Further documents are listed in the continuation of box C.

☒ Patent family members are listed in annex.

* Special categories of cited documents:

- *A* document defining the general state of the art which is not considered to be of particular relevance
- *E* earlier document but published on or after the international filing date
- *L* document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)
- *O* document referring to an oral disclosure, use, exhibition or other means
- *P* document published prior to the international filing date but later than the priority date claimed

- *T* later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
- *X* document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
- *Y* document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.
- *&* document member of the same patent family

Date of the actual completion of the international search

8 September 2004

Date of mailing of the international search report

17/09/2004

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INTERNATIONAL SEARCH REPORT

International application No.
PCT/US2004/012780

Box II Observations where certain claims were found unsearchable (Continuation of item 2 of first sheet)

This International Search Report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☒ Claims Nos.:
because they relate to subject matter not required to be searched by this Authority, namely:
Although claim 15 is directed to a method of treatment of the human/animal body, the search has been carried out and based on the alleged effects of the compound/composition.
2. ☐ Claims Nos.:
because they relate to parts of the International Application that do not comply with the prescribed requirements to such an extent that no meaningful International Search can be carried out, specifically:
3. ☐ Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box III Observations where unity of invention is lacking (Continuation of item 3 of first sheet)

This International Searching Authority found multiple inventions in this International application, as follows:

1. ☐ As all required additional search fees were timely paid by the applicant, this International Search Report covers all searchable claims.
2. ☐ As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.
3. ☐ As only some of the required additional search fees were timely paid by the applicant, this International Search Report covers only those claims for which fees were paid, specifically claims Nos.:
4. ☐ No required additional search fees were timely paid by the applicant. Consequently, this International Search Report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

- ☐ The additional search fees were accompanied by the applicant's protest.
- ☐ No protest accompanied the payment of additional search fees.

INTERNATIONAL SEARCH REPORT

Information on patent family members

International Application No
PCT/US2004/012780

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